actively cooling said interior wall using a cooling fluid; and

forming a thermal bridge within a gap between said heat transfer members and said interior wall by said medium wherein heat is transferred from said heat transfer member through said thermal bridge to said interior wall.

89. The method of claim 88, further comprising:

actively cooling said heat exchange structure using a cooling fluid. --

Remarks

By the instant Amendment, Claims 36-40, 44-62, 64-66 and 68 have been canceled and new claims 69-89 have been added to more clearly define the invention. Allowance of the above-identified application in view of the new claims and following remarks is respectfully requested.

Preliminarily, Applicants thank the Examiner for his courtesies during the telephonic interview on Friday, January 4, 2002. During the interview, Applicants, through their attorneys, discussed the inventive concept of a thermal bridge and proposed claim language reflecting the same. Applicants also discussed the absence of the formation of a thermal bridge by the prior art.

I. Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 36-40, 44-62, 64-66 and 68 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing

to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Although these claims are canceled by the instant amendment, Applicants herein attempt to clarify and eliminate any confusion with respect to the terms "thermal bridge" and "biopharmaceutical products."

A. Rejection of the Term "Thermal Bridge"

The Office Action reads that the term "thermal bridge" is vague because "[i]t appears to denote any area where one thermally conditioned surface is in greater proximity to another surface (either itself thermally conditioned or unconditioned) than it is to other surfaces within the device." Also, the Office Action reads that "the entire content of fluid in the tank will conduct heat out of the medium if it is cooler than the medium."

New claim 69 recites that one or more heat transfer members allow a thermal bridge to formed by a medium comprising a biopharmaceutical product in a gap between the heat transfer member and the interior wall wherein heat is transferred from the heat transfer member through the thermal bridge to the interior wall in response to the interior wall being actively cooled. Thus, the thermal bridge is not merely "any area where on thermally conditioned surface is in greater proximity to another surface," as set forth in the Official Action. Rather, the thermal bridge as claimed requires heat to be transferred therethrough in a particular way, e.g. from the heat transfer member to the interior wall.

Applicants also respectfully submit that the Specification enables persons of ordinary skill in the art to determine how the heat exchange structure must be positioned within the interior

cavity in order to form a thermal bridge by the medium between one or more of the heat transfer members and the interior wall. Specifically, the Specification provides at page 6, lines 8-14 the following:

> In general, the system should be constructed such that the distance to be bridged by the thermal transport bridge will be a function of the thermal properties of the medium and the system, manufacturing requirements and construction processes used to build the system, and other relevant parameters of the system and components used. The size of the gap to be filled by the bridge can be determined through simple trial and error.

The Specification further provides, on page 6, lines 23-27, clear examples of how close the heat exchange members may be.

If, however, the gap between the heat transfer member and the interior wall is too large, a thermal transfer bridge will never form, even if the entire medium in the gap is frozen. If the gap is too large, then a location between the heat transfer member and the interior wall will have a higher temperature than the heat transfer member and the interior wall, even if the medium in the gap is frozen, and not a downward temperature gradient from the heat transfer member to the interior wall as characterized by a thermal transfer bridge, e.g. as depicted in Fig. 3(b) of the present application. Thus, if the gap is too large, heat is not transferred from the heat transfer member through the medium in the gap to the interior wall. Rather, heat is transferred from the medium at a location in the gap to the interior wall and to the heat transfer member. In other words, heat is being extracted from a location in the gap between the heat exchange member and the interior wall, not from the heat transfer member to the interior wall as required when a thermal

bridge is formed. Thus, as compared to, for example, the downward temperature gradient from the heat transfer member to the interior wall shown in the temperature profile in Fig. 3(b), a temperature profile of the device disclosed in the Wisniewski and Wu publication would show the temperature gradually increasing after the fin to a location in the gap between the fin and the interior wall and then gradually decreasing towards the interior wall. In fact, even after the medium in the gap is frozen, the temperature at a location between the fin and the interior wall is still higher and heat is transferred from this location in the gap to both the fin and interior wall. Therefore, no thermal bridge is formed by the device disclosed in the 1992 Wisniewski and Wu publication. A Declaration of Richard Wisniewski will be filed shortly hereafter in support of this argument along with schematic representations of the temperature distributions of the device disclosed by the Wisniewski and Wu publication before and after the medium freezes.

Accordingly, Applicants respectfully submit that the term "thermal bridge" is definite.

B. Rejection of the Term "Biopharmaceutical Product"

In the Office Action, the Examiner states the term "biopharmaceutical product" as it is used in the application is ambiguous. Applicants respectfully traverse this rejection.

As provided in the Specification, Applicants recognized, among other things, that the apparatus and method according to the aspects of the present invention is suited for use in processing biopharmaceutical products, as that term is understood by those of ordinary skill in the art. For example, the recited

apparatus and method promotes uniform freezing at a rapid pace which allows the biopharmaceutical product in the container to be frozen in as close to its native state as possible. (Specification, page 7, lines 17-19). Additionally, the present invention allows the freezing process to be done in a repeatable fashion so that a user can be assured that the freezing process is not causing batch to batch variations in the product. (Specification, page 7, lines 19-21).

Applicants respectfully submit that improper processing of biopharmaceutical product by, such as, for example, freezing and thawing, destroys biopharmaceutical products. In contrast, other products, such as, for example, orange juice, milk, water, particulate materials, and comestibles do not have the same processing concerns as biopharmaceutical products. In particular, the method or apparatus used to process (e.g. freeze or thaw) these other products is not critical and will not destroy these other products.

The term "biopharmaceutical product" as set forth in the Specification on page 20 includes, but is not limited to, proteins, cells, antibodies, medicines, plasma, blood, buffer solutions, viruses, serum, cell fragments, cellular components, and any other biopharmaceutical product. Applicants also provided a definition of a "biopharmaceutical product" in a previous Amendment dated April 13, 2000 as "a product derived from biological sources that has an intended therapeutic application and whose manufacturing is or will be regulated by pharmaceutical or veterinary regulatory agencies." This definition is supported by the Declarations of Chris J. Burman, V. Bryan Lawlis, Jr., and David A. Vetterlein ("the Declarants"),

who are considered by Applicants as persons of ordinary skill in the art.

Despite support of the aforementioned understanding of the term of "biopharmaceutical products" from three persons of ordinary skill in the art having over 72 years of experience in the biotechnology and biopharmaceutical industry, the Official Action, as read, erroneously complicated the well recognized understanding of this term. For example, the Office Action sets forth an opinion in concluding that orange juice is a biopharmaceutical product. In particular, in the Office Action on page 7, it states that "[t]he chances of the FDA regulating 'buffer solutions' as a pharmaceutical in the future would be about on par with the chances of the FDA regulating orange juice as a biopharmaceutical *in the Examiner's opinion*" (emphasis added). Based on such reasoning,,the Official Action indicates that the definition offered by the Declarants appears to be "unworkable in the Examiner's opinion." (See page 8 of the Office Action).

Applicants, however, recognize that, for example, a "buffer solution" can indeed be a biopharmaceutical product depending upon the contents of such a solution. It is really apparent that buffer solutions which are biologically based may indeed be regulated and be a biopharmaceutical product. Moreover, buffer solutions which are not biologically based are not biopharmaceuticals. Applicants respectfully submit that if, for example, a particular buffer solution is not derived from biological sources nor regulated by FDA, then it would not be considered a biopharmaceutical product under the aforementioned understanding of the term. It is well known in the art that certain buffer solutions, for example, blood and other body

fluids are indeed biopharmaceutical products due to mixtures of weak acids and bases present in them. Once one recognizes that the list of potential biopharmaceutical products set forth in the specification sets forth examples of products which may be biopharmaceuticals, it is readily apparent that the rejection should be withdrawn.

Therefore, Applicants respectfully traverse the opinion set forth in the Office Action that orange juice, milk, water, comestibles, particulate materials and any other non-biopharmaceutical product disclosed by the cited references on which are relied upon in rejecting the claims in the outstanding Office Action, are considered a biopharmaceutical product. To maintain such a rejection, the Office, under M.P.E.P. § 2144.04, must be supported by a reference or affidavit in support of such position and opinion or in contradiction to the above definition and Declarations by three Declarants of ordinary skill in the art.

Moreover, as stated in a previous Amendment, any of the exemplary biopharmaceutical products provided in the Specification, or any other biopharmaceutical products, must be a biopharmaceutical product according to the above definition, having the same processing concerns. Applicants respectfully submit that one of ordinary skill in the art is capable of distinguishing and classifying which products are and are not biopharmaceutical products based on the above definition, as evidenced by, for example, the Declarants classification of milk and orange juice as not being pharmaceutical products in their Declarations. For example, one of ordinary skill in the art is capable of determining which proteins, cells, antibodies, medicines, plasma, blood, buffer solutions, viruses, serum, cell

fragments, cellular components, and any other biopharmaceutical product are considered a biopharmaceutical product under the above definition.

Finally, Applicants object to the reliance in the Office Action on an interpretation of a "would-be infringer" in rejecting the term "biopharmaceutical products." Under M.P.E.P. § 2173.02, definiteness of claim language must be analyzed in light of the content of the particular application disclosure, the teachings of the prior art and the claim interpretation that would be given *by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.* Applicants respectfully submit that the proper inquire is how "biopharmaceutical product" will be interpreted by a person of ordinary skill in the art, not a would be infringer.

Accordingly, Applicants respectfully submit that the term "biopharmaceutical product" is definite.

C. Rejection of Claims 49-54, 59-62 and 64-66

Claims 49-54, 59-62 and 64-66 were also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because they appear to be claiming features not found in the elected species of Figure 5.

By the instant Amendment, Claims 49-54, 59-62 and 64-66 have been canceled and new claims 69-89 have been added. Applicants respectfully request examination and allowance of new claims 69-89.

II Rejections under 35 U.S.C. § 103(a)

Claims 36-40, 44-62, 64-66 and 68 were rejected under 35 U.S.C. § 103(a) as obvious over the 1992 publication by Wisniewski and Wu in view of United States Patent No. 3,308,552 to Kaufman et al, United States Patent No. 5,220,954 to Longardner and GB 845,576 to Richelli.

By the instant Amendment, Claims 49-54, 59-62 and 64-66 have been canceled and new claims 69-89 have been added. No new matter has been added.

Applicants' invention recited in claim 69 is directed to an apparatus for processing a biopharmaceutical product comprising a vessel adapted to receive a medium comprising a biopharmaceutical product. The vessel comprises an interior wall defining an interior cavity. The interior wall is adapted to be actively cooled using a fluid. The apparatus further comprises a heat exchange structure within the cavity having one or more heat transfer members. The heat exchange structure is positioned within the cavity wherein one or more of the heat transfer members allow a thermal bridge to be formed by the medium between the one or more heat transfer members and the interior wall wherein heat is transferred from the heat transfer member through the thermal bridge to the interior wall in response to the interior wall being actively cooled.

Claim 88 is directed to a method of processing a biopharmaceutical product comprising the step of forming a thermal bridge formed by the medium between the one or more heat

transfer members and the interior wall wherein heat is transferred from the heat transfer member through the thermal bridge to the interior wall.

With respect to an obviousness rejection, Applicants submit that a valid obviousness rejection requires that the prior art references, when combined, teach or suggest all of the claimed elements. In the instant application, however, there are features of Applicants' claims which are not taught or suggested by the applied references, either individually or in combination. For example, Applicants respectfully submit that the Wisniewski and Wu publication, Kaufman, Longardner and Richelli, alone or in combination, fail to disclose or suggest, at least, a thermal bridge formed by a medium comprising a biopharmaceutical product between one or more heat transfer members and the interior wall of a vessel wherein heat is transferred from the heat transfer member through the thermal bridge to the heat transfer member of the interior wall when the interior wall is actively cooled as recited in the claims.

As the Examiner recognized, the Wisniewski and Wu publication discloses only fins extending from the heat transfer coil towards the wall of the container. Applicants respectfully submit that the Wisniewski and Wu publication does not disclose or suggest, at least, the formation of a thermal transfer bridge formed by a medium comprising a biopharmaceutical product as recited in the claims. As explained above in clarifying the term "thermal bridge," the medium at a location in the gap between the fins and the interior wall of the device disclosed in the Wisniewski and Wu publication has a higher temperature than the fins and the interior wall, even if the medium in the gap is frozen. In other words, at no time is there a downward

temperature gradient from the fin to the interior wall as required by a thermal transfer bridge.

Moreover, contrary to the Examiner's indication during the telephonic interview that it may be obvious to extend the fins of the device disclosed by the 1992 Wisniewski and Wu publication to aid in the formation of compartments, the Wisniewski and Wu publication teaches away from extending the fins towards the interior wall. Specifically, the publication teaches that the heat transfer fins "were configured to divide the tank volume into compartments to decrease freezing and thawing time and to reduce cryoconcentration effects." See pg. 136, col. 1. Thus, the Wisniewski and Wu publication already teaches that the fins aid in forming compartments and there is no need to extend the fins towards the walls. There is simply no suggestion or motivation therefore to extend the fins of the device disclosed by the 1992 Wisniewski and Wu publication towards the interior wall.

Moreover, assuming arguendo that there is a motivation within the references to extend the fins, there is simply no teaching or suggestion to extend the fins to a point where a thermal bridge, as claimed, in formed. None of the references recognizes the advantages of a thermal bridge and/or the problems or disadvantages of freezing without the formation of a thermal bridge. Because the references do not recognize the advantage of forming a thermal bridge, there is simply no motivation or suggestion to one of ordinary skill in the art to arrive at the claimed invention.

The combination of Kaufman, Longardner, and Richelli with the Wisniewski and Wu publication fails to cure this deficiency.

Specifically, Kaufman, Longardner and Richelli fail to disclose or suggest, at least, a medium comprising a biopharmaceutical product or a thermal transfer bridge formed by the medium between the one or more heat transfer members and the interior wall wherein heat is transferred from the heat transfer member though the thermal bridge to the interior wall when the interior wall is actively cooled as recited in the claims.

Furthermore, there is no suggestion or motivation for combining the Wisniewski and Wu publication with Kaufman, Longardner or Richelli or any other cited reference in the Office Action. "Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." M.P.E.P. §2143.01. The Office Action merely points to the purported disclosure of certain individual claim elements in each reference and then, without more, concludes that it would have been obvious to one of ordinary skill to combine these references. This is insufficient. See In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a prima facie case of obviousness was held to be improper.).

Specifically, none of the cited references suggested to be combined with the Wisniewski and Wu publication disclose or suggest biopharmaceutical products, recognize the problems associated with processing biopharmaceutical products or a thermal transfer bridge formed by a medium comprising a

biopharmaceutical product between a heat transfer member and the interior wall.

In contrast, Kaufman discloses a freeze-drying apparatus for the dehydration of any particulate material (e.g. peas, berries, grapes, diced fruits, vegetables, meats, milk, eggs, and juices). (Col. 4, line 67 to Col. 5, line 4). However, a particulate material is not considered a biopharmaceutical product in accordance with the principles of the present invention. Even if particulate materials considered biopharmaceutical products (not admitted), there is no disclosure or suggestion in Kaufman of a thermal bridge formed by the particulate material between the fins and the interior surface of the drying chamber wherein heat is transferred from the fins through the thermal bridge to the interior surface when the interior surface is actively cooled. Further, the apparatus disclosed in Kaufman has baffles 15 extending from the interior surface of the drying chamber. These baffles are described as serving to "transfer heat to the material being dried" and "supporting the material and to direct the movement of the particles of material as the drying chamber rotates." (Kaufman, Col. 3, lines 49-53), with no teaching that a thermal bridge is formed by the particulate material between the fins and baffles. Finally, since Kaufmam does not disclose or suggest biopharmaceutical products, it also does not recognize the problems associated with processing such products to provide a motivation or suggestion to combine with the Wisniewski and Wu publication.

Longardner discloses a heat exchanger for a phase change material, such as hydrated salt phase change compositions (Col. 1, lines 40-42). However, hydrated salt phase change compositions are not considered biopharmaceutical products in

accordance with the principles of the present invention. Even if the compositions where considered biopharmaceutical products (not admitted), there is no disclosure or suggestion in Longardner of a thermal bridge formed by the compositions between the fins and the interior surface of the chamber wherein heat is transferred from the fins through the thermal bridge to the interior surface when the interior surface is actively cooled. Further, since Longardner does not disclose or suggest biopharmaceutical products, it also does not recognize the problems associated with processing such products to provide a motivation or suggestion to combine with the Wisniewski and Wu publication.

Richelli discloses a mould having flanges extending inwardly within the mould for the production of ice blocks (Col. 1, lines 35-36). However, water or ice is not considered a biopharmaceutical product in accordance with the principles of the present invention. There is also no disclosure or suggestion in Richelli of a heat exchange structure within the interior cavity having one or more heat transfer members or a thermal bridge. Further, since Richelli does not disclose or suggest biopharmaceutical products, it also does not recognize the problems associated with processing such products to provide a motivation or suggestion to combine with the Wisniewski and Wu publication.

The other references relied on in the Office Action, namely United States Patent No. 983, 466 to Voorhees (Apparatus for Ice Making), United States Patent No. 3,318,105 to Burroughs (Apparatus for Producing Clear Ice), and United States Patent No. 2,129,572 to Finnegan (Means for Freezing and Preserving Comestibles), also do not disclose or suggest a medium comprising a biopharmaceutical product or a thermal transfer bridge formed

by the medium between the one or more heat transfer members and the interior wall wherein heat is transferred from the heat transfer member through the thermal bridge to the interior wall when the interior wall is actively cooled as recited in the new claims. Applicants respectfully submit that the mere formation of ice about freezing elements which eventually connects to ice formed on another freezing element as, for example, disclosed in Voorhees and Burroughs, is not a thermal transfer bridge according to the principles of the present invention because heat is not necessarily transferred from one freezing element through a thermal bridge to the other freezing element when the interior wall is actively cooled. Further, none of these references recognize the problems associated with processing biopharmaceutical products to provide a motivation or suggestion to combine with the Wisniewski and Wu publication.

For these reasons, it is believed that all of the claims as presently presented, are patentable, and that this application is in allowable condition. Accordingly, allowance of the claims 69-89 is respectfully requested.

Respectfully submitted,

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